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DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

CONTENTS:

ACUTE EFFECTS OF HISTAMINE IN PSYCHIATRIC PATIENTS 259
John W. Lovett Doust

VARIATIONS IN RAPID COMA TECHNIQUE OF CARBON DIOXIDE INHALATION THERAPY 269
Albert A. LaVerne

HYPNOTHERAPY FOR THE CONTROL OF ANXIETY 274
Jerome M. Schneck

ISONICOTINIC ACID HYDRAZIDE IN NONTUBERCULOUS MENTAL PATIENTS 278
W. P. Wilson

EFFECT OF PROLONGED ADMINISTRATION OF PITRESSIN ON THE BLOOD PRESSURE IN PSYCHOTIC PATIENTS 280
D. E. Macdonald

NEUROLOGICAL CLINICAL PATHOLOGICAL CONFERENCE 282

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DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Acute Effects of Histamine in Psychiatric Patients

(Their Significance for Therapy)

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Toronto, Canada

The mechanisms underlying the relationship between the intravenous injection of small quantities of histamine and the subsequent predictable development of headache have been well summarized recently by Wolff (1948). It has been established beyond all doubt that the histamine headache is associated with vasodilatation of the intracerebral blood vessels (Forbes *et al.*, 1929; Pickering and Hess, 1933; de Seze, 1938; Koopmans, 1939; Ogawa, 1940; Obrador and Alvarez, 1946) and with an increase following upon an initial decrease, in the cerebral blood flow (Forbes *et al.*, 1929; Schmidt, 1934; Keller, 1939; Gorev, 1945; Wolff and Cattell, 1948). It is postulated that the expansion of the relaxed pain-sensitive dural and pial vessels (Wolff, 1948, p. 167) or perhaps of the larger cerebral arteries (Pickering, 1939; Friedman *et al.*, 1945) is responsible for the actual headache. Concomitantly with the changes in cerebral blood flow there occur also changes in the arterial pressure, the consistent fall of 10-40 mm. Hg. which takes place some 20 seconds after the histamine injection being replaced by a return to normal or "slightly higher than normal" (Wolff, 1948, p. 166). It would appear that the headache is maximal when the secondary blood pressure rise is also at its height (Wolff, 1948, p. 169) and the cerebral blood flow is greatest (Forbes *et al.*, 1929). Pickering and Hess (1933) noted that raising the arterial pressure intensified the headache and Friedman and Brenner (1944) in their experiments were impressed by the finding that the blood pressure often rose significantly above the resting pre-injection level following its initial fall in response to intravenous histamine.

Intravenous histamine has been employed by a number of workers as a therapeutic measure in psychiatry (Hill, 1938, 1940, 1944; Marshall and Tarwater, 1938; Marshal, 1939; Robb *et al.*, 1940; Mieer, 1948; Sackler, *et al.*, 1949a and b, 1951) and even as a treatment for various forms of headache (Horton *et al.*, 1939; Horton, 1941a and b; Rainey, 1943; Thomas and Butler, 1946). The apparent paradox implied by the juxtaposition of these facts is resolved in part by the conclusion of Wolff (1936) that a drop in arterial pressure to a critical level, no matter what the cause, produces a dilatation of cerebral blood vessels and, further, that the mechanism of the headache following the intravenous exhibition of histamine is identical with that of the headache associated with anoxaemia, whatever the cause of the anoxaemia may be (Wolff, 1948, p. 205).

The widespread role of anoxia in psychiatry has often been referred to (e.g. Pickworth, 1937; Danziger, 1945; Hoskins, 1946) but less often demonstrated (Tsikhanshkaya, 1948; Lovett Doust, 1951a, 1952a).

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The differential incidence of chronic recurrent headaches among psychiatric and healthy populations is however well established (Wolff, 1948; Lovett Doust, 1952b), as is that for migrainous types of vascular headache (Lennox, 1941; Lovett Doust, 1952b). Wolff (1948) is cautious in evaluating the possible significance of endogenous histamine in "psychogenic" headache but suggestive is von Storch's experimental study (1940) in which he found the histamine headache threshold to be considerably lower in subjects given to chronic recurrent headaches and to migraine than it was in healthy controls not prone to headaches.

Ray (1946) employed a reduction time technique (Vierordt, 1878) of spectroscopic oximetry and found a significant positive relationship between this variable and the alveolar oxygen tension, the B.M.R. and the arterial blood pressure recordings (Ray *et al.*, 1946). Further work has demonstrated (Lovett Doust, 1951a and b) a highly significant correlation between these reduction time measurements and arterial oxygen saturation values. A principal point in favour of the spectroscopic oximetry method is that it is rapid and readily repeatable, thus enabling serial estimations to be made in a short time interval within minimal discomfort to the subject.

The present paper reports an investigation into the oximetric correlates of the sphygmomanometric changes accompanying the production of histamine headache in patients with a variety of psychiatric disorders. The purpose of the study was to attempt the further resolution of the anoxic implications of histamine with regard to its use as a treatment for mental disease.

PROCEDURE

A series of 46 psychiatric patients was examined. The patients were all drawn from the wards of the Maudsley and Bethlem Royal Hospitals; they fell into four main diagnostic groups. The *neurotic* group included two males and six females with an average age of 30.75 (range 17-44) years; it comprised five anxiety states and three hysterics. The *depressive* group was composed of five males and nine females with an average age of 47.14 (range 29-62) years and included eight agitated and four retarded psychotic depressions together with two examples of reactive depression. The *schizophrenic* group included three males and eleven females with an average age of 29.64 (range 15—51) years; it was subdivided into six cases of paranoid schizophrenia, four of hebephrenia and four catatonic schizophrenics in stupor. A fourth *"organic"* group was also tested. This consisted of six males and four females whose average age was 58.43 (range 51-68) years. All were patients showing some degree of presenile dementia, the pathological basis of which was vascular in seven cases, Alzheimer's disease in two and a cerebral tumour in one.

Each patient was investigated individually, and simultaneously by two observers. The task of one of these latter was to administer the injection and measure the blood pressures; the responsibility of the other was to make oximetric estimations of the arterial oxygen saturation. Both examiners also recorded separately their observations of the patients' reactions, complaints and changes in psychophysical status. Arterial pressures were measured by means of a mercury sphygmomanometer, the cuff of which was secured around the upper right arm of the subject. Sufficient preliminary readings were always taken before each experiment commenced in order to ensure a stable baseline. The oximetric status was determined by the present writer's modification (Lovett Doust, 1952a) of Ray's (1946) "reduction time" technique, the results being expressed as "R.T. seconds," convertible into percentage arterial oxygen saturation values by means of a regression equation (Lovett Doust, 1951b). The site of examination was the nail fold skin of the subject's left ring finger after this had been prepared by histamine ointment inunction and a sphygmomanometer bandage had been wrapped around the left upper arm and connected to a pressure bottle. Illumination was held constant and note was taken of the time of disappearance of the alpha and beta absorption bands as observed through a Beck pocket prismatic spectroscope after occlusion of the peripheral circulation. As with the sphygmomanometric estimations, several observations were made initially until a stable baseline was obtained with read-

ings which checked to within 1 R.T. sec.

Following the establishment of baseline conditions, 0.1 mgm of histamine* was injected into one of the ante-cubital fossa veins of the subject's right arm and a stop watch started. Arterial pressure and spectroscopic oximetric estimations were then conducted simultaneously at 15 secs. and at 1 min. from the time of injection and thence at 1 min. intervals until the subject had returned to his pre-injection status both objectively and subjectively. Such simultaneous recordings enabled correlations of the variables to be subsequently carried out with confidence.

Following the plan of Igersheimer and Stevenson (1951), who evaluated the effects of electroshock treatment on blood pressure levels by employing the Hines-Brown cold pressor test as an index of reactivity, a group of psychiatric patients was given intravenous histamine before and after various other psychiatric treatments. A total of 19 patients was assessed in this way and, of these, six were examined before and after lobotomy, ten before and after shock treatment (nine receiving a minimum of eight electroshocks and the remaining patient 32 insulin coma treatments) and three before and after a 3-months period of intensive psychotherapy. The lobotomy and shock treatment patients were examined exactly three weeks after the conclusion of their treatment procedure. The lobotomy patients included five cases of chronic affective disorder, depression, and one of schizophrenia, paranoid type; the shock treatment patients consisted of five cases of affective disorder, depression, three of catatonic schizophrenia and two of schizophrenia, paranoid type; the patients receiving psychotherapy were all psychoneurotics, two of whom were classified as hysterics and one as a neurotic depression.

RESULTS

These are shown in Figure 1 and in Tables 1-5. They are divided for convenience into the three "phases" defined by Pickering (1939) to describe the sequence of changes following the intravenous exhibition of histamine. *Phase I* is characterized by a dilatation of small cerebral blood vessels, a fall in the cerebral arterial pressure and a rise of intracranial pressure; *Phase II* by a return of the arterial and intracranial pressures towards normal as the dilatation of the small vessels subsides. Expansion of the larger arteries is accompanied by headache, maximal in this phase; *Phase III* represents subsidence of the headache as the relaxation of the intracerebral arteries passes away.

The sequence of events following intravenous histamine administration is given in Fig. 1. Here it is seen that the three phases of the arterial pressure response are accompanied closely by similar phases of the oximetric response, both in the direction and quantification of the changes and in the time relationships involved. Headache occurred predictably with recovery from the initial hypotension of Phase I, and could be anticipated either from a knowledge of the preceding pattern of change of the arterial pressure or from that of the arterial oxygen saturation values. Fig. I also demonstrates that the mean rise in Phase II is to levels well above the resting values both sphygmomanometrically and oximetrically. That this rise is statistically significant is confirmed in Table 3 in which the mean figures given represent differences in each case from the resting level values. Table 3 also shows that although these differences are significant in all four diagnostic groups studied (and hence of course also for the total group means given in Fig. I), there is no essential

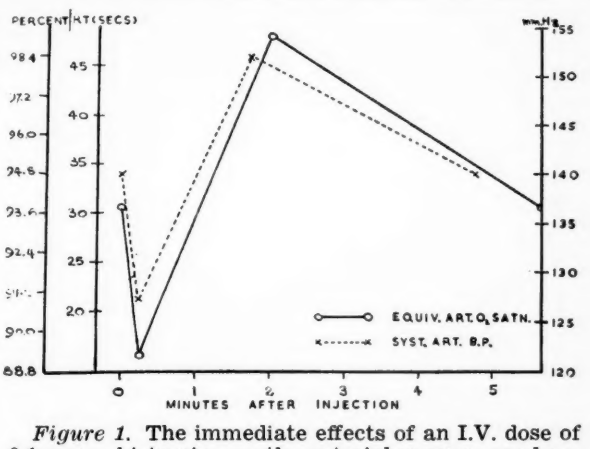

Figure 1. The immediate effects of an I.V. dose of 0.1 mgm. histamine on the arterial pressure and arterialized capillary oxygen saturation. Headache appeared following the depressor phase and was maximal at the second minute.

*Histamine acid phosphate "Sterules Martindale," manufactured by Savory and Moore, Ltd.

TABLE 1

PRE-INJECTION PHASE

	Neurotics (8)	Depressives (14)	Schizophrenics (14)	Organics (10)	Analysis of Variance F-ratio	P	eta²
Arterial O_2 satn. (per cent.)	95.3	92.9	90.0	98.9	—	—	—
R.T. (secs.)	35.750	27.643	18.143	47.600	6.529	.01	.318
B.P. (mm Hg)							
—systolic	128.250	130.286	127.000	181.600	8.709	<.001	.383
—diastolic	75.750	84.857	76.000	107.800	6.169	.01	.301
—pulse pressure	52.500	44.000	51.000	73.800	5.294	.01	.311

Mean resting baseline status of the four diagnostic groups of 46 psychiatric patients. An analysis of variance shows them to be differentiated significantly in all modalities tested. A product moment correlation coefficient was run on the total group with respect to the resting oximetric and systolic arterial pressure values. It yielded an r=+.536. With (n—2) degrees of freedom, t is 5.220 indicating a highly significant correlation between these two variables (P <.001).

TABLE 2

EFFECT OF INTRAVENOUS HISTAMINE—PHASE I

		t tests Neurotics	Depressives	Schizophrenics	Organics	Analysis of Variance F-ratio	P	eta²
R.T. diffs. (15 secs.)	D	—23.000	—13.393	—5.615	—22.000			
	S	8.944	6.446	4.900	26.948			
	d.f.	7	13	12	9	3.440	.05	.201
	t	6.801	7.488	3.970	2.449			
	P	<.001	<.001	.01	.05			
B.P. (systolic)	D	—8.000	—10.220	—13.000	—17.890			
	S	9.789	10.839	—	18.974			
	d.f.	2	8	1	8	<1.0	N.S.	—
	t	1.154	2.654	—	1.665			
	P	N.S.	.05	—	N.S.			
B.P. (diastolic)	D	—1.333	—10.222	—10.000	—13.111			
	S	1.011	10.443	—	14.110			
	d.f.	2	8	1	8	<1.0	N.S.	—
	t	1.865	2.755	—	2.615			
	P	N.S.	.05	—	.05			

In this and in Tables 3 and 5, D=mean difference; S=standard deviation; d.f.=degrees of freedom; t=t ratio; and P=confidence level of statistical probability.

TABLE 3

EFFECT OF INTRAVENOUS HISTAMINE—PHASE II

Group:		t tests Neurotics	Depressives	Schizophrenics	Organics	Analysis of Variance F-ratio	P	eta²
R.T. diffs. (maximum rise)	D	+13.250	+15.000	+15.929	+27.200			
	S	4.815	10.812	9.215	30.986			
	d.f.	7	13	13	9	1.340	N.S.	.09
	t	7.283	5.000	6.230	2.633			
	P	<.001	<.001	<.001	.05			
B.P. systolic diffs. (maximum rise)	D	+15.250	+11.000	+13.143	+11.889			
	S	10.680	9.664	12.095	11.489			
	d.f.	7	13	13	8	<1	N.S.	—
	t	3.760	3.953	3.774	2.912			
	P	.01	.01	.01	.02			
B.P. diastolic diffs. (maximum rise)	D	+12.000	+3.429	+9.714	+5.330			
	S	11.212	4.182	8.071	9.747			
	d.f.	7	13	13	8	<1	N.S.	—
	t	2.818	2.848	4.151	1.539			
	P	.05	.02	.01	N.S.			

TABLE 4

TIME RELATIONSHIPS, PHASES II AND III

GROUP	PHASE II Mean time to max. change (mins.) OXIMETRY Time	OXIMETRY S	ARTERIAL PRESSURE Time	ARTERIAL PRESSURE S	PHASE III Mean time to resting levels (mins.) OXIMETRY Time	OXIMETRY S	ARTERIAL PRESSURE Time	ARTERIAL PRESSURE S
Neurotics (8)	1.50	0.500	1.75	0.707	4.75	1.854	5.25	1.615
Depressives (14)	2.00	0.707	1.79	1.121	5.50	1.341	4.29	1.684
Schizophrenics (14)	1.50	0.627	1.29	0.726	5.07	2.283	5.21	3.423
Organics (10)	2.90	1.446	2.11	2.238	6.80	2.786	4.00	4.000
Analysis of Variance F=	5.344		1.056		1.698		<1.0	
P=	.01		N.S.		N.S.		N.S.	
eta²=	.276		.070		.108		—	

Times are expressed in minutes as the interval elapsing between the injection of histamine and the phase of response in question. Time to Phase I was arbitrarily taken to be be 15 secs.

TABLE 5

EFFECT OF SHOCK TREATMENTS, LOBOTOMY AND PSYCHOTHERAPY ON THE HISTAMINE RESPONSE

TYPE OF TREATMENT		DIFFERENCES FROM RESTING VALUES R.T. (secs.) Pre- minus Post-Treatment differences 1st 15 secs. fall	Max. rise	B.P. (mm Hg) Pre- minus Post-Treatment differences Systolic—Max. rise	Diastolic—Max. rise
Shock (course of insulin coma or electroshock)	D	+9.88	—1.9	+3.80	+3.80
	S	5.92	5.70	10.67	3.84
	d.f.	7	9	9	9
	t	4.412	1.00	1.01	2.81
	P	.01	N.S.	N.S.	.05
Lobotomy	D	+1.00	—5.67	+5.67	—0.33
	S	15.81	8.73	4.54	13.97
	d.f.	5	5	5	5
	t	.14	1.45	2.79	.06
	P	N.S.	N.S.	.05	N.S.
Psychotherapy (3 months)	D	—4.00	+2.33	—10.00	—9.33
	S	4.55	5.56	4.32	0.95
	d.f.	2	2	2	2
	t	1.24	.59	3.27	13.95
	P	N.S.	N.S.	N.S.	.01

In this Table the effects of various treatments are shown as differences (Pre- and Post-treatment) of differences (from resting values) for the oximetric and arterial pressure monitoring variables.

difference between the groups so far as the responses in Phase II are concerned. This finding is in contrast to the responses in Phase I (Table 2) for here it can be seen that the mean fall in oximetric values (although not the fall in arterial pressure) is significantly less in the schizophrenic and depressive, i.e. in the psychotic groups, than it is in the neurotic and organic patients. A similar dichotomy of group differentiation is seen in the time relationships of Phases II and III (Table 4). Here again the diagnostic groups differ significantly from one another oximetrically, whereas they behave more homogeneously with regard to the arterial pressure variable.

Table 1 indicates that differentiation of the four diagnostic groups is highly significant with respect to their baseline pre-stress resting levels, no less for the arterial pressure than for the oximetric variable. This finding confirms the similar differential status reported in a former series of cross-sectional studies (Lovett Doust, 1952a) wherein it was shown that constitutional schizophrenics show an oximetric anoxaemia at rest, in "organic" cases the oximetric levels are high while results in cases of psycho-

neurosis or affective disorder, depression, fall within the normal or low normal range. The finding that the four groups can also be differentiated on the basis of their resting arterial pressures is not surprising in view of Ray's (1946) significant positive correlation coefficient between these two variables, confirmed in this present report.

Table 5 gives the statistical analysis of the results of the impact of four different varieties of accepted psychiatric treatments on the response to intravenous histamine administration. It will be seen that in general the findings agree with those of Igersheimer and Stevenson (1951) in that what influence there is, is small. In the case of the shock treatments, it does however appear justifiable to conclude that the patient's homeostatic responses are significantly greater than they were before the therapy was applied, since both phases I and II are affected in the direction of greater reactivity. If histamine "biochemotherapy" (Sackler *et al.*, 1951) be assumed to represent a legitimate therapeutic procedure in psychiatry, then it may be concluded from these findings that the effects of treatments in mental disorder are additive with respect to improvement in homeostatic equilibrium. This conclusion has been empirically accepted by many clinicians in any event as regards electroshock, insulin coma therapy and psychotherapy, any two or all three of which are often advocated together in the treatment of many mental disorders.

DISCUSSION

Factors Common to Successful Treatment in Psychiatry

The cycle of events illustrated for intravenous histamine in Fig. I, with oximetric and arterial pressure measurements as the monitoring variables, represents a sequence found also when these variables are investigated in other therapeutic methods. The effects of electroconvulsive therapy (E.C.T.) or metrazol on the arterial blood pressure are to produce an initial relative hypotension a few seconds after the stimulus is applied, followed by an after-rise usually to levels above resting values (Jackson and Jackson, 1938; Gellhorn and Darrow, 1939; Bini and Puddi, 1940; Delay, 1946). Because of mechanical difficulties the initial hypotensive phase is not readily picked up but the hypertensive phase immediately following it has been amply confirmed (Accornero, 1940; Deshaies and Renault, 1948; Igersheimer and Stevenson, 1951). Furthermore, Igersheimer and Stevenson (1951) found that these immediate arterial pressure responses to E.C.T. are similar whether the patients are suffering from schizophrenia, manic-depressive psychosis or involutional melancholia. As with the effect on blood pressure responses, so also with the effect on the arterial oxygen saturation levels. There is reliable evidence to prove that the application of both metrazol and electroshock in animals and man is followed by a "Phase II" increase in cerebral metabolism (Davis *et al.*, 1944); Stone *et al.*, 1945; Geiger and Magnes, 1947; Klein and Olsen, 1947; Danziger and Kindwall, 1948). In man this is shown by an increase in the basal metabolic rate following the shock (Gerard, 1938a and b; Low *et al.*, 1938; Katzenelbogen *et al.*, 1939). The initial "Phase I" effect of anoxaemia preceding this increase has been demonstrated for both metrazol and electroshock by Himwich and Fazekas (1942) and for metrazol convulsions in schizophrenic patients by Loman and his co-workers (1940), who showed that the blood oxygen content fell during the fit, reaching its lowest level at the end of the seizure. As the convulsion passes away, the stage of hyperpnoea is accompanied by a rise in blood oxygen values to well above the original resting level (Phase II). This finding is paralleled in animals by the morphological reports of Alexander and Löwenbach (1942, 1943, 1944) who noted a transient blanching of the capillary bed, confined to the path of the current, in cats subjected to electroshock. That this cycle of changes, and especially the anoxaemia, is not entirely due to the physical activity accompanying the fit, is shown by the fact that initial cerebral hypoxia occurs even in animals paralysed with erythroidin and maintained by artificial respiration (Davis *et al.*, 1944; Davies and Remond, 1947).

Identical patterns of change, but on a more extended time base, are seen in patients subjected to insulin hypoglycaemia.

Here, of course, the transition from Phase I to Phase II and III is accomplished by the administration of glucose or other carbohydrate, rather than spontaneously by the subject as in histamine therapy, metrazol and electroshock. Clinically, however, it is no uncommon observation that it may also take place after a spontaneous convulsion occurring during the course of hypoglycaemia. With regard to the blood pressure response, the consensus of opinion (Gellhorn, 1943) seems to be that during the hypoglycaemia, a fall occurs with a widening of the pulse pressure (Weichmann and Koch, 1929; Ernstene and Altschule, 1931; Ernstene *et al.*, 1935). Zimmermann (1938) and Georgi (1939) found that the arterial pressure changes run parallel with those of the blood sugar. Cerebral metabolism is likewise depressed, cerebral oxygen utilization, as measured by the arterio-venous oxygen difference, falling progressively as the hypoglycaemia becomes more profound (Dameshek and Myerson, 1935; Himwich *et al*,, 1939). Oximetric techniques, measuring arterial oxygen saturation values in the peripheral blood, also reveal a similar anoxaemia (Lovett Doust and Schneider, 1952a) and this despite the increases in blood flow and temperature of the skin of the extremities (Gellhorn, 1943). The oximetric monitoring technique also demonstrates the rise in oxygen saturation which takes place in Phase II after interruption of the hypoglycaemia, and which we have referred to as the "rebound phenomenon" (Lovett Doust and Schneider, 1952a), after Gerard (1938a).

Vascular changes in the cortical areas of living brains of monkeys and rabbits during hypoglycaemia were photographed by Baruk and his co-workers (1942-45; 1948). During insulin coma the brain appeared pale and anæmic with collapse of the cerebral blood vessels; with reversal of the coma following glucose administration the brain regained its colour and the vessels became full once again. The same technique employed with metrazol showed an initial transient constriction of the vessels which was followed by an extreme vasodilatation.

The essential similarity between the effects of hypoglycæmia and anoxia has been stressed both by Gellhorn (1943) and by Himwich (1951). The correlation between oxygen saturation (cerebral metabolism) and arterial blood pressure is important since the variations of the cerebral blood flow are regulated in large part by the systemic arterial pressure (Forbes, 1940; Himwich, 1951). If not in many respects (Gellhorn, 1943), then at least in their capacity to induce a rebound phenomenon, metrazol and electroshock resemble the similar effects of anoxia and hypoglycæmia and Bellinger and his co-workers (1943) have thrown doubt on the earlier report of Fraser and Reitman (1939) concerning the efficacy of nitrogen inhalation therapy. Even the treatment of Loewenstein (1945), whatever its bearing on his theory of bacillary thrombi (1944), reproduces the sequence of events of the rebound phenomenon by the cycle of lowering the arterial pressure initially by amyl nitrite inhalation and following then by an intravenous adrenaline injection. The rebound phenomenon is seen also in other treatments for which success has been claimed in psychiatry, e.g. in fever therapy (Alagia and Flannery, 1937) in the exhibition of barbiturates (Dameshek *et al.*, 1934) and in the recent Swedish trial of intravenous malononitrile, a substance alleged to increase nucleo-protein production and which causes an initial increase in schizophrenic symptomatology. The worsening of the clinical condition is reversed, often with improvement in the psychosis, following the interruption of the drug's action by sodium thiosulphate (Hyden and Hartelius, 1948). It may be presumed for many others, e.g. Fiamberti's intravenous acetylcholine treatment (Cohen *et al.*, 1944), psychotherapy (Flinker, 1938; Hoagland *et al.*, 1938; Lovett Doust, 1951b; Lovett Doust and Leigh, 1952), the Russian technique of hæmocolloidoclastic shock (quoted by Cobb, 1947) and sleep (Kessler and Gellhorn in Gellhorn, 1943; Lovett Doust and Schneider, 1952b). Finally it is perhaps relevant to mention that the grand mal convulsion of the idiopathic epileptic patient may be considered on this view as a naturally occurring homeostatic episode in a constitutionally predisposed subject which improves his cerebral metabolism by the self-induction of a rebound phenomenon.

SUMMARY

(1) A total of 46 psychiatric patients suffering from psychoneurosis, affective disorder, depression, schizophrenia and "organic" syndromes of cerebrovascular and Alzheimer's disease were assessed oximetrically by a spectroscopic technique and sphygmomanometrically both before and after the intravenous administration of 0.1 mgm. histamine. A further 19 patients were similarly assessed separately before and three weeks after courses of shock treatments and psychotherapy, and after lobotomy, in order to evaluate any change in homeostatic reactivity resulting from the treatment.

(2) It was found that significant differences existed between the various diagnostic groups with regard to their resting oximetric status, their systolic and diastolic arterial pressures, and their pulse pressures. It was also found that a significant correlation exists between spectroscopic oximetry measurements and the arterial pressure.

(3) Responses of the patients to intravenous histamine were similar for the oximetric and sphygmomanometric monitoring variables, an initial fall (Phase I) being followed by a (Phase II) supra-normal rise ("rebound phenomenon") before a return to resting values occurred (Phase III). Headache was predictably maximal at the height of Phase II.

(4) The effects of shock treatment included an increased homeostatic reactivity to histamine.

(5) The implications of these results are discussed in relation to the possible significance of the rebound phenomenon in psychiatric treatment.

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Variations in Rapid Coma Technique of Carbon Dioxide Inhalation Therapy

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High concentrations of carbon dioxide in oxygen mixtures consisting of over 40 per cent carbon dioxide to induce rapid coma was first reported by this author in 1952. In 1929, Loevenhart et al., Meduna in 1948, and others have stressed the hazard of administering over 40 per cent carbon dioxide to patients. However, their conclusions are not based upon experience with humans. On the contrary, my experience has demonstrated that high concentrations of carbon dioxide even 95 per cent to induce rapid coma of brief duration are safe and at the same time therapeutically more effective than the low concentrations previously used. No toxic or other serious irreversible effects utilizing the high concentrations of carbon dioxide in rapid coma techniques have been noted in over 20,000 treatments. Rapid coma is therefore a radical departure in theory and practice from all previously described carbon dioxide therapies.

Differentiation Between Rapid Coma and Slow Coma Techniques

Slow Coma Techniques: In these techniques the carbon dioxide concentration is not higher than 40 per cent in oxygen mixtures. The patient breathes the gas for 20 to 50 consecutive breaths, which produces gradual physiological changes of prolonged duration lasting from the induction stage, through coma, and finally to the return of full consciousness. This method was first reported by Loevenhart et al. in 1929 with 40% carbon dioxide in oxygen mixtures and used only on psychotics. In 1937, Kerr first reported the use of 30% carbon dioxide-70% oxygen mixture on anxiety states in neurotics. In 1948, Meduna reported the use of 20 to 30% carbon dioxide in oxygen mixtures on a larger variety of neurotics. Subsequent modifications of Meduna's method by others utilize sub-coma doses or introduce pure carbon dioxide into the breathing bag after 15 to 20 breaths of the 20-30% mixture to an undetermined and unknown concentration of carbon dioxide in order to produce a deeper coma. For example, Meduna's multiple breath technique of 30% carbon dioxide in oxygen mixtures requires an average of three minutes for 30 consecutive breaths to produce coma, the return to full consciousness requires two minutes, for a total of five minutes.

Rapid Coma Techniques: In these techniques the carbon dioxide is of high concentration, above 40 per cent, usually between 70 to 95 per cent carbon dioxide in oxygen mixtures. These high concentrations of carbon dioxide are introduced to the respiratory tract suddenly so that *rapid* physiological changes of *brief duration* are produced to sub-coma or coma levels and to the return of full consciousness. Rapid coma techniques were first reported by LaVerne in 1952. For example, a single breath of 70% carbon dioxide in oxygen mixtures (single breath technique with breath holding) is forcibly inhaled by the patient producing unconsciousness in eight seconds, and a return to full consciousness in 22 seconds, for a total of 30 seconds.

Variations in Technique of Rapid Coma

Single Breath Rapid Coma Technique: As reported by LaVerne in 1952 this technique consists of a forced inhalation of a single breath of 70% carbon dioxide and 30% oxygen mixture preceded by a forced exhalation of room air producing a rapid coma of brief duration. In the single breath technique combined with voluntary breath holding, the patient who has just completed inhaling the single breath of carbon dioxide as in the above mentioned single breath technique is encouraged to retain the gas as long as he is physically able. Such retention of the inhaled gas even if only for a few seconds produces a much greater absorption and saturation of carbon dioxide in the blood stream

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via the pulmonary circulation. This is equivalent to the production of a much deeper physiological effect including coma than is otherwise possible by the single breath technique alone.

Multiple Breath Rapid Coma Technique Using High Concentration of Carbon Dioxide Preceded by Nitrous Oxide Anaesthesia: Carbon dioxide therapy preceded by nitrous oxide anasthesia was first reported by Meduna in 1952. This modification of Meduna is readily applicable to rapid coma carbon dioxide techniques. The patient breathes 100 per cent nitrous oxide for approximately one minute until the anesthesia is sufficiently deep so that he will not become too apprehensive when the more irritating high concentration of carbon dioxide is administered immediately afterwards. The optimum level of nitrous oxide anesthesia is the beginning of snoring or trembling of the body. A common error is to administer the carbon dioxide before the patient is sufficiently anesthetized. This error may produce treatment anxiety and may frighten the patient. At all events the therapist must hold the breathing mask firmly and should not be prevented from completing the carbon dioxide administration by the patient's actions or movements while under anaesthesia. A separate face mask and breathing bag which has been previously titrated with the high concentration of carbon dioxide in oxygen mixtures (which will replace the nitrous oxide unit) is immediately applied to the patient's face after the patient has been anaesthetized. Positive pressure is applied by manually pressing the carbon dioxide breathing bag in order to insure constancy and purity of the inhaled mixture and to prevent exhaling into the breathing bag. The exhaled gases of the patient are discharged through a three way valve.

In switching from the nitrous oxide to the carbon dioxide breathing bag, the patient should not be permitted to inhale more than two breaths of room air, since the room oxygen inhaled into the patient's pulmonary system will materially dilute the concentration of the carbon dioxide subsequently applied and thus reduce its therapeutic effectiveness. (Patients who complain of nausea or emesis following nitrous oxide anaesthesia may be medicated with dramamine prior to therapy.)

The number of carbon dioxide breaths should be from four to twelve for a 95 per cent mixture. The best therapeutic results are obtained with six to nine breaths for this mixture. The criterion for the optimum number of breaths is the production of a physiological level of coma with mild twitchings or mild clonic movements of face and body lasting approximately ten to fifteen seconds. The therapist should avoid production of a deep generalized convulsive level unless the more superficial levels of coma have been clinically inffective after a preliminary trial of five to ten treatments. Lower concentrations of carbon dioxide are less effective therapeutically than the optimum concentration of 95 per cent in five per cent oxygen mixtures. The therapist is cautioned against use of 100 per cent of carbon dioxide as this constitutes a physical hazard. However, the presence of five per cent oxygen is safe and without hazard provided the therapist initiates only two breaths of this concentrated mixture at the first treatment in order to observe the physiological level of coma which is induced, and then gradually increases the number of carbon dioxide breaths with each successive treatment until optimum physiological level of coma is produced. This gradual method is also a safeguard in revealing idiosyncracies to carbon dioxide and nitrous oxide which although rare, may exist. The shallow breathers require more breaths of carbon dioxide than the deep breathers. This technique produces a rapid coma of a longer duration than that produced by the single breath technique alone, but relatively of briefer duration than that produced by the conventional carbon dioxide methods of Meduna and others. After the administration of carbon dioxide is completed, nitrous oxide may be applied for less than one minute at the discretion of the therapist. However I have seldom found it necessary to re-apply nitrous oxide anaesthesia except in patients who manifested persistent severe abreaction anxiety.

The convulsive levels reached with multiple breath technique inducing rapid coma with high concentration of carbon dioxide are more intense than those induced by the

multiple breath 30 per cent mixtures of Meduna. These rapid coma convulsions more closely resemble the decerebrate fits induced by electrical, insulin, and metrazol shock. However, they are not as exhausting nor as violent as the fits induced by these latter methods nor do they produce memory changes. I have encountered no complications such as fractures, fatalities etc. in the rapid coma convulsions. Prior to the convulsions the patient may undergo a period of apnea lasting a few seconds. He then goes through a brief tonic phase which lasts from two to five seconds and then proceeds into the clonic phase which may be generalized and may last from one-half to one and one-half minutes. During the entire convulsive period the patient breathes and does not become as cyanotic as in the more violent electric or insulin convulsive treatments. The recovery period is about five minutes after which the patient may go home. For the deeper physiological rapid coma techniques including convulsive, the therapist should use precautions as he would with conventional convulsive therapies such as prevention of tongue biting, respiratory stimulants, oxygen, etc. It is possible for some patients to breathe directly high concentrations of carbon dioxide without previous nitrous oxide anaesthesia in order to produce rapid coma. However, the majority of patients will require previous nitrous oxide anaesthesia for the multiple breath rapid coma technique.

Number and Frequency of Treatments, and Indications That Determine the Specific Variation of Rapid Coma Technique to Be Used.

The multiple breath rapid coma technique preceded by nitrous oxide anaesthesia is therapeutically the most effective variation of all rapid coma techniques. This technique should be administered in gradually increasing doses until optimum physiological level of coma is produced. If there is no clinical improvement in 20 treatments, then five additional deeper physiological treatments should be attempted. The absence of clinical response then warrants discontinuance of treatment. Treatments are administered three times weekly. If there is clinical improvement, then the frequency is reduced to twice weekly after the first 25 treatments, for an additional 15 treatments, and then finally tapered off to once weekly for a total of 50 treatments. Refractory cases, especially schizophrenics, should be given multiple treatments. There may be as many as three treatments per session and may even be administered daily, provided there is at least a five minute interval between treatments. Clinical response is frequently expedited in difficult cases by administering such multiple treatments per session, and should be employed before therapy is abandoned.

Patients who can not tolerate the multiple breath rapid coma technique preceded by nitrous oxide may be treated with the single breath rapid coma techniques with or without breath holding. Frequency and number of treatments is similar to that described in multiple breath rapid coma technique above.

Patients may be alternated with above variations according to discretion of the therapist.

Titration of High Concentration Carbon Dioxide in Oxygen Mixtures

I recommend high concentrations of carbon dioxide (60 to 95%) in oxygen mixtures for the variations of rapid coma technique. An average mixture of 70 per cent carbon dioxide 30 per cent oxygen is used in the single breath technique and titrated in an eleven liter breathing bag. If the patient is a shallow breather a higher concentration of carbon dioxide such as 90 per cent is required in single breath technique, whereas in the deep breathers a concentration of 70 per cent may suffice. The determining criterion is the production of an adequate physiological coma. One 40 liter breathing bag filled with the high concentration of carbon dioxide in oxygen is sufficient for one to three complete multiple breath rapid coma treatments. It is recommended that a 40 liter breathing bag be used in the multiple breath rapid coma technique. Such a bag is available commercially.

The specific percentage concentration must be determined by the therapist by repeated trials using a flow-meter and visibly titrating the degree of inflation of the breathing

bag by each component gas. In order, he introduces 100 per cent oxygen into the breathing bag which expands to a certain configuration; then he shuts off the oxygen and introduces 100 per cent carbon dioxide to a visibly determined full capacity of the breathing bag. Errors of five to ten per cent are not harmful so long as there is at least approximately five per cent oxygen in the breathing bag.

Rationale of Rapid Coma Techniques and its Variations

In rapid coma, there is induced a high speed physiological change, so that the adaptive mechanisms of the body resistances are minimized and do not tend to obstruct or inhibit the action of carbon dioxide upon the tissues.

The sudden saturation of the blood and body fluids with carbon dioxide in such a relatively short space of time produces greater physiological and endocrinological changes than hitherto possible with the slow coma methods of Meduna and others.

The high concentration of carbon dioxide introduced suddenly into the respiratory tract and circulation precipitates an intense stress reaction stimulating the body defenses to go into action; preliminary laboratory studies suggest pituitary-adrenal stimulation.

Low oxygen tension (hypoxia) is known to produce marked changes in cerebral function, especially to increase intracranial vasodilation. The low oxygen component in rapid coma technique is further lowered by preceding nitrous oxide anaesthesia, thus producing a relatively higher ratio of carbon dioxide in the tissues which may at the same time tend to enhance the physiological action of carbon dioxide in tissues.

Psychologically there is an intense fear of death in some patients who verbalize, "I thought I was dead," "I feel that I have expiated my guilt feelings."

Advantages and Disadvantages of Rapid Coma-Techniques

Advantages

1. Psychological Advantages: Minimization of the psychologic fears usually associated with carbon dioxide inhalation therapy of the multiple breath technique of Meduna:

a. A fear of suffocation or air hunger sensation, which is frequently encountered in the induction phase of the multiple breath technique.

b. Apprehension of the day of treatment.

c. Treatment anxiety that develops during the course of carbon dioxide inhalation therapy of the Meduna multiple breath technique (from ten to 20 treatment).

2. Physiological Advantages: There is less physical exhaustion with the single breath rapid coma technique. It is physiologically impossible to raise the overall concentration of carbon dioxide in the blood to the toxic or harmful levels, since only a single breath is inhaled into the lungs, and only a part of it is absorbed into the pulmonary circulation, then rapidly diluted in the large blood volume of the body fluids, and quickly blown off via the lungs when the mask is removed.

3. Technical Advantages: Less gas is consumed and less time is required than in the multiple breath technique of Meduna and others.

Disadvantages of the Rapid Coma Techniques

Commercially mixed gases of the 70 or more per cent carbon dioxide mixtures are not available in a single tank.

The greater complexity in filling the breathing bag with the proper mixture, since there may be error of five to 15 per cent. However, such a range of error is not serious or harmful provided there is at least five per cent oxygen in the breathing bag.

In the multiple breath technique inducing rapid coma with high concentration of carbon dioxide it is more difficult for the patient to undergo the transition from nitrous oxide to the high concentration of carbon dioxide. In the Meduna multiple breath technique with 30 per cent carbon dioxide, the transition from nitrous oxide to carbon dioxide is smoother. In the rapid coma nitrous oxide technique it may be necessary to utilize restraints or have them available for immediate use at the transition stage from nitrous oxide to carbon dioxide and during the abreactive stage. In most patients no restraints will be required. The degree of abreaction in single breath technique with or without breath holding does not anticipate the degree of abreaction that

may occur in the deeper physiological techniques.

Contraindications: These are similar to those described by Meduna in the multiple breath technique, namely, severe hypertension, pulmonary tuberculosis, coronary heart disease, severe emphysema.

Overtreatment and Treatment Anxiety

Treatment anxiety is a form of sensitization of the body to carbon dioxide which occurs from the tenth to 20 treatment with the conventional methods of Meduna and others. It is important to differentiate this treatment anxiety from the anxiety caused by the irritative effects of higher concentrations of carbon dioxide upon the mucous membranes which produces a sensation of suffocation and is frequently encountered at the pre-coma level.

As deeper physiological levels of rapid coma carbon dioxide therapy are achieved, treatment anxiety may be greater. In single breath technique with breath holding, treatment anxiety is rare and can be avoided by reducing treatments to a maximum of two per day. In multiple breath rapid coma technique preceded by nitrous oxide anaesthesia anxiety is a greater risk and should be recognized by the therapist. It can be avoided or minimized by reducing the number of inhalations during treatment or by alternating with single breath technique. In the deeper physiological levels of multiple breath technique with high concentration of carbon dioxide, there are some patients in whom such convulsive treatments produce a discharge or amelioration of anxiety and others in whom the reverse is true. It is therefore incumbent upon the therapist to proceed cautiously and skillfully. A basic principle in carbon dioxide therapy is to fit the therapy to the patient. A minimal of anxiety is frequently present during a course of treatment with rapid coma multiple breath technique. This should not deter the therapist from continuing both with intensity of dosage and frequency of treatment. If optimum coma level is not produced, the goal of therapy will not be achieved.

For hypersensitivity to carbon dioxide which is characterized by deep coma and severe convulsive reactions produced by relatively few breaths of carbon dioxide, and for treatment anxiety which threatens to become a management problem, the following procedures are recommended:

a. Sedate mildly with barbiturates and administer anti-convulsant medication as Dilantin, etc.
b. Prescribe calcium ion in the form of calcium lactate or other calcium preparation, 1-3 gms. daily.
c. Finally, if necessary, gradually reduce the carbon dioxide concentration and add more oxygen to the mixture.

Results

Patients that may benefit by rapid coma techniques are primarily the psychoneurotic. These consist of anxiety states, phobics, conversion hysterias, psychosomatics, neurotic homosexuals, and neurotic alcoholics. The rapid coma techniques have not yet been used sufficiently to permit adequate evaluation of their long range therapeutic effectiveness. A substantial number of patients previously treated unsuccessfully with Meduna's multiple breath technique manifested significant clinical improvement with the rapid coma techniques up to one year follow-up. Similar clinical improvement was noted in a large series of patients treated solely with the rapid coma techniques.

Favorable clinical response was obtained in a significant number of obsessive compulsives, psychotic depressions, and schizophrenics treated with the multiple breath rapid coma technique preceded by nitrous oxide. These psychiatric diseases have heretofore been resistant to the technique of Meduna and others. The preliminary results for this group are encouraging, since they were previously unsuccessfully treated with electro and insulin shock. However, enthusiasm should be tempered with further scientific evaluation, follow-up studies, and by confirmation from other workers.

Conclusions

1. My experience demonstrates that the clinical results wih rapid coma techniques of carbon dioxide therapy are superior to those that I have achieved with the slow coma conventional techniques.

2. A new variation of rapid coma technique is introduced, namely, the multiple breath rapid coma technique preceded by nitrous oxide, which appears to be therapeutically more effective in a larger variety of psychiatric diseases than heretofore

achieved with other types of carbon dioxide therapy.

3. However, follow-up studies in these cases treated with the rapid coma techniques have not been of sufficient duration to permit final evaluation.

4. Rapid coma techniques of carbon dioxide therapy are without hazard provided the contraindications are observed.

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Hypnotherapy for the Control of Anxiety

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Observations have been gathered over a period of years in connection with the efficacy of hypnosis in the control of anxiety. In varying degree the subject has been alluded to by others in papers and books. I have dealt with this issue, in part, with stress on specific points of interest. For example, in one paper a patient with recurrent anxiety episodes was described and the method of treatment was outlined pointing up the psychodynamics and their clarification with the eventual relief of the recurrent episodes.[1] Another report dealt with a very ill patient who was experiencing considerable conscious anxiety in addition to other problems.[2] The point stressed there was the change in findings on psychological testing when pre-treatment and post-treatment rec-

ords were evaluated. A third report dealt also with relief from anxiety which was experienced consciously after acute onset and in that paper attention was focused not only on pre-treatment and post-treatment psychological test records, but also on the changes discernible in psychological data when it was gathered under hypnosis as compared with the waking state.[3]

At this time I am reporting on a series of patients whose records were culled from a larger number where similar hypnotherapy had been employed. The focus now is upon the clinical psychiatric changes in relation to the anxiety aspects of the patient's difficulties, and in each instance certain additional implications are stressed pertaining to treatment process or its effects which merit attention for therapists undertaking hypnotherapeutic work.

Case I: The first patient, a 48-year old man, sought hypnotherapy specifically after a series of psychoanalytic experiences over the years. His attitude toward psychoanalysis and psychiatry in general was hostile. He expressed a desire for symptom relief only. Hypnotherapeutic sessions were held two or three times a week for several weeks. The approach used was one of stressing the relaxation aspects of the procedure with suggestions for a carry over of its tension releasing results into his everyday living. His anxiety was extreme and the wording of suggestions had directly to do with a lessening of this anxiety. In addition there were suggestions pertaining to the decrease in other symptoms. His attitude toward the therapist and toward treatment was consistently ambivalent with varying degrees of verbalization of this ambivalence. Reduction in his consciously experienced persistent anxiety was achieved almost from the start, although it had been present for at least twenty to twenty-five years. At times he appeared to minimize the importance of this relief and at other times he spontaneously expressed a grateful feeling. Additional wording of hypnotic instructions had to do with his working both consciously and unconsciously on his problems but verbalization of any insights was not stressed and this assumed no place of importance in his treatment. The fact to be stressed is the achievement of relief from anxiety beyond what would ordinarily be expected under such circumstances after many years of previous psychiatric treatment attempts. Furthermore, it is to be noted that with some relief from anxiety the patient spontaneously mentioned an improvement in his interpersonal relations. The nature of this improvement was not clarified fully. Such changes evidently result from an unconscious reorganization of psychological functioning, the details of which we do not adequately understand.

Case II: This patient was 43 years old. He had experienced the onset of sudden, severe anxiety 21 years previously under circumstances which were recalled. The anxiety had not abated. It was so marked that speech patterns were disrupted and he would stammer frequently. For years he suffered from profuse perspiration which literally would drip down his face and invariably cause comment by observers. He was regarded by family and acquaintances as an oddity. It became apparent early in treatment that goals would have to be restricted because of his intellectual limitations, severe psychological rigidities, and stunted opportunities for development based on socioeconomic and cultural considerations. The first few contacts with him did not involve hypnosis but a series of weekly contacts thereafter did involve its use at his request. The approach with this man was similar to the previous case insofar as stress on the relaxation aspects was concerned. During the first few sessions he was given the opportunity to speak freely about anything he wished and he could do this much better than in the ordinary waking interview. He verbalized some feelings of guilt regarding isolated experiences and discharged emotional tension in showers of tears. The approach subsequently in hypnosis involved suggestions for over-all feelings of improvement and relief from anxiety. To the amazement of family and acquaintances the perspiration problem was obliterated and the dissipation of conscious anxiety was remarkable. But along with this, there occurred the problem to be noted especially. Whereas the patient's anxiety was so pronounced heretofore, the deep hostilities which he harbored could not be verbalized adequately and

had to be considerably suppressed or repressed, although they were still in evidence. With the dissipation of conscious anxiety he expressed and acted out his deep hostilities to the point where his poor interpersonal relations became even more disrupted. Whereas previously his rage had been deeply internalized with marked self-destructive results, it now could be expressed outwardly to a much greater extent. Lacking in proper defenses to cope with it, and deficient in the psychological complexities of more mature functioning, his immediate family in particular received the brunt of his aggression. The quality of the latter was not novel, but its quantitative aspects produced repercussions. This does not argue against the use of hypnotherapy of this type under such circumstances, but it does point up considerations to be taken into account. The remaining details in the problem are much more complex and the issues involved were being dealt with concurrently with his wife who was also in treatment. Similar problems occur, of course, in therapy which does not involve the use of hypnosis. In addition, the onset of the severe acting out problems did not occur at the same time that the anxiety was being reduced. They occurred after an interval when the patient found that he could express hostility considerably without a return of the intolerable feeling associated with consciously experienced anxiety.

Case III: The patient, 28 years old, sought treatment because of very marked conscious anxiety of at least six years' duration. He claimed it was so great that at times he could not speak. This was quite evident because he would block repeatedly and his sentences were practically disjointed at times. Accompanying this, he displayed facial grimacing which was practically schizophrenic-like. He maintained he could not concentrate on reading, barely could understand what people were saying at times, could not lead a reasonable social life and was severely handicapped in business. Although treatment progressed on an insight-level, it dealt mainly with conscious and pre-conscious data. There was no relief from anxiety for several weeks without the use of hypnosis. When hypnotherapy was initiated the patient expressed an instantaneous change. His hypnotizability was variable from week to week. He was superficially passive-dependent in his approach, but attempted more subtly to be controlling insofar as the very induction procedure was concerned and the defining of the verbal instructions during the hypnosis. In general the suggestions were limited to encouraging an over-all feeling of well being with a carry-over between sessions, and to this were added in various modifications suggestions regarding improvements in functioning in social and business situations. With his marked relief from anxiety, his speech patterns improved greatly, the grimacing faded from the picture, a feeling of mental clarity was expressed, and his contacts with people improved. He was particularly impressed by the hypnotherapy as a turning point in the treatment setting.

Case IV: A 30-year-old patient had been troubled by feelings of anxiey for three years. The first part of his treatment contact did not involve hypnosis. Although various aspects of his background and current involvements were explored there was essentially no change in his feelings. His ability to work on an insight level seemed limited and finally little more than symptom relief was attempted. With the onset of hypnotherapy a rewarding degree of anxiety reduction was achieved and a pattern of intermittent anxiety feelings was experienced during each day. The improvement appeared to level off in this way until it was decided to teach the patient self-hypnosis in order to encourage a greater degree of involvement on his part in treatment and in order to see whether additional results could be achieved. The patient would fail to utilize the technique from time to time and this appeared to be in keeping with some of his masochistic tendencies into which he had gained just a little insight. The relief achieved then varied with his use of the method and it varied too with the time and interest that he devoted to it. When this became clear to him he participated more fully. The result was a consistent decrease in the anxiety. Instead of episodes appearing several times a day, they decreased to once a day, then once every few days, once a week, and then

at infrequent intervals. With the initiation of a conditioning process through the self-hypnosis, a post-hypnotic reaction set in so that tension relief could be achieved frequently simply by thinking about and momentarily re-experiencing a self-hypnotic state.

Discussion

Experience with the four patients presented here and with others points to several issues in connection with such treatment in psychiatry. The use of hypnosis in the relief of anxiety may help produce results even in the face of symptomatology persisting over twenty or more years. Obtaining a good result in such instances may frequently be difficult to predict and a trial at treatment is therefore warranted. Hypnotherapy appears to be a more potent therapeutic tool in achieving such relief from anxiety when compared with other methods. Relief from one symptom may often be accompanied by relief from others, especially when a similar or the same dynamic core plays a role in them. This may be observed too at times in therapeutic work which does not involve hypnosis. Relief from anxiety is beneficial often in other ways when such tension dissipation permits, for example, easier expression in inter-personal relations. Occasionally difficulties occur as in one of these cases when hostility held in check is turned toward others rather than toward the self. This is a problem of treatment in general rather than hypnotherapy specifically, but it must be evaluated carefully because of relative potency of hypnotic techniques. With some patients symptom change may occur immediately. With others, several sessions are required. The degree to which various aspects of behavior are affected by modifications in ego functioning and defense structure apparently varies from case to case. In the same way, the degree of relief from anxiety varies from patient to patient. The use of self-hypnosis to supplement hypnotherapeutic sessions should be considered at times. This use may be concurrent with initial hypnotherapeutic efforts in regular sessions or may follow the regular hypnotherapy contacts when the effects of the latter have levelled off.

The degree to which insight therapy is attempted will depend not only on the apparent capacities of the individual patient but on his expressed desires based on a variety of past conditionings and current needs. An initial symptom relief approach may at times open the way for more extended and involved treatment. Relief from anxiety may at times be a necessity before the patient will even permit further exploration. As is well known, however, relief from anxiety may, without the presence of additional motivation, forestall interest in further therapeutic effort.

The wording of suggestions and the complexity of the therapeutic approach are based on the intelligence and emotional status of the patient, preconceptions regarding hypnotherapy, and past experiences. For one patient a suggestion to the effect that anxiety will decrease and disappear may be all that he would expect. To another such a suggestion may appear ridiculous unless worded in a more involved fashion. Yet the essence of what is said may be similar in both instances as may also be the results. At times this may relate to the level of intellectual functioning but not always. Thus the capacity to assimilate a complex thought process and series of verbalizations may be present, but the hostility to such complexity based on emotional reactions to treatment which had previously been conditioned by unfavorable experiences may result in the patient's favoring simple, precise suggestions carrying implications only for the most superficial level of functioning.

In view of the frequency of complaints of anxiety by patients as described in these cases, the potentialities of hypnotherapy in such goal-limited contacts should be widely recognized.

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Isonicotinic Acid Hydrazide in Nontuberculous Mental Patients

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Robitzek et al. in reporting the effect of isonicotinic acid hydrazide in the treatment of tuberculosis have commented on the marked mental changes observed in patients receiving this drug.[1] Depression, anorexia and asthenia seen in severely debilitated tuberculous patients are frequently replaced by euphoria, increase in appetite, and increased activity. Concomitantly evidences of central nervous system and sympathetic autonomic stimulation occur as side effects of the drug.[2] More recently, marked behavioural changes have been observed in schizophrenics following treatment with the drug. These changes were thought to be more than a transient feeling of euphoria and were said to be indicative of a renewed contact with reality.[3]

Although the reported personality changes were not observed in all patients (normal and mentally ill), they occurred frequently enough to indicate the possibility of a central cerebral stimulative effect. Evidence to support this view gained support from the observation that frequently mental changes occurred before the drop in temperature. Because of these observations it was thought that the drug offered therapeutic possibilities in the treatment of mental illnesses, occurring in the nontuberculous patients, in which the symptoms of anorexia, depression or refusal to eat were prominent.

Method

Twelve nontuberculous chronically depressed anorexic, or catatonic patients and eight acutely depressed anorexic patients were selected for this study. All patients were residents in the State Hospital at Butner, North Carolina and the Psychiatric Section of the Duke Hospital at Durham, North Carolina. All patients were physically normal and showed no roentgenographic evidence of tuberculosis. A complete blood and urine examination was done before the drug was given. The dosage of isonicotinic hydrazide used was 3 to 4 mgm/kilo/day. This was the dosage used in the treatment of tuberculous patients who had shown the changes previously described.[1] During the period of treatment all patients were observed daily for the effect of the drug on mood, appetite, and side effects. The patients were weighed every other day. All subjects received a standard hospital diet of approximately 2400 to 2600 calories plus whatever extra food was requested by the patient. They were informed prior to the institution of the study that they might ask for extra trays or extra servings of food if they so desired. Treatment was terminated at the end of three weeks.

Results

Diagnostic classification of the patients is summarized in Table I. In only one of the 20 patients treated with this drug was there any change in either mood or appetite which was thought to be related to the drug. This acutely depressed patient within 24 hours following the first dose of the medication stated that she felt much better and began to eat large quantities of food. She rapidly gained weight during the next two weeks. Cessation of the administration of the drug brought about no reappearance of her previous symptoms. Five of the subjects complained of the side effects of the drug. Constipation was noted in three patients and vertigo in two. There were no symptoms of sympathetic stimulation. No changes in the schizophrenic symptoms were observed.

Discussion

The mechanism of action in the production of the symptoms of anorexia and mood disturbances in tuberculosis is not well understood. Whether the toxins produced by the tubercle bacillus are responsible for the changes is at best a debatable point. The dramatic changes observed in patients with tuberculosis seem to be related to the effect of the drugs on the tuberculous process and

From Duke University School of Medicine.

not to the central nervous system effect of isonicotinic acid hydrazide.

The failure of this drug in the dosages used here to produce any changes in 19 of 20 patients would indicate that it does not offer any therapeutic possibilities in mental diseases. It is quite possible that the one patient who seemed to respond to the drug would have remitted spontaneously had she not received the drug since her illness was of short duration and was relatively acute. The lack of change in schizophrenic symptomatology does not corroborate the observations of Kreiser et al.[3]

An investigator working in the Duke Psychiatric Clinic is using this drug in higher doses and has some evidence that there might be favorable response in mild depressive states. This work however is not complete and an adequate evaluation as to the efficacy of the drug cannot be made at present.[4]

Summary

(1) Isonicotinic acid hydrazide was administered to 12 non-tuberculous patients with chronic depressive illnesses and 8 non-tuberculous patients with acute depressive illnesses. All patients were anorexic and showed depressed mood. Dosages used were 3 to 4 mgm/kilo/day given over a three week period.

(2) Minor side effects were infrequently seen.

(3) 19 of 20 patients showed no change in the symptomatology of their disease. The improvement in the one patient may have been coincidental and cannot be ascribed to the use of the drug.

(4) Changes in appetite and mood observed in tuberculous patients receiving isonicotinic acid hydrazide are probably not related to any central nervous system effect.

TABLE I

DIAGNOSES

CHRONIC	
Schizophrenic Reaction	7
Schizoaffective Type	
Schizophrenic Reaction	2
Catatonic Type	
Psychotic Depressive Reaction	2
Chronic Brain Syndrome	1
Associated with Senile Brain Disease	
Depressed Type	
	12
ACUTE	
Psychotic	6
Depressive Reactions	
Psychoneurotic	2
Depressive Reactions	
	8
TOTAL	20

Author's Note: The isonicotinic acid hydrazide (Rimofon) used in this study was generously supplied by the Hoffman LaRoche Co. of Nutley, N. J.

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Effect of Prolonged Administration of Pitressin on the Blood Pressure in Psychotic Patients

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Pitressin is one of the relatively pure fractions of posterior pituitary extract. It is known that in man a single injection of pitressin is followed by a rise of blood pressure, which may be preceded by an initial depressor effect. It is also known that repeated injections of pitressin are followed in experimental animals by a fall in blood pressure (inversion effect) which is due to cardiac dilation.

In this hospital, pitressin is administered to selected patients in a dose of 10 units daily at first for 10 days, thereafter the same dosage on alternate days as long as may be required. The blood pressure is estimated three times daily for three weeks before commencing the pitressin, and three times daily for one month after commencing. It was therefore considered that an estimation of the effect of continuous pitressin administration on the blood pressure could be made by a comparison of these two records.

Under normal physiological conditions, the blood pressure may fluctuate markedly. (Best and Taylor: Physiological Basis of Medical Practice, 1944, page 212.) For example there is a normal diurnal variation of five to ten mm., reaching its peak in the afternoon. Digestion also influences the systolic pressure to a small but definite extent, there being a rise of six to eight mm. following a meal and persisting for about one hour. Emotional influences and exercise also affect the systolic pressure, and a fall of 15 to 30 mm. occurs in quiet sleep. However, in disturbed sleep, the pressure may rise to as much as 200 mm. systolic, and 105 mm. diastolic.

Hypertension may be said to exist if the systolic pressure is 15 mm. above, and diastolic pressure 8 mm. above the average for the person's age (Best and Taylor: Physiological Basis of Medical Practice, 1944, page 215).

The average readings in young persons are: Systolic 90 to 120 mm.; Diastolic 60 to 80 mm. The average reading for 60 years is: Systolic 135, Diastolic 87 mm.

After consideration of the foregoing, it was decided that a variation of 10 mm. or less in the systolic pressure after administration of pitressin could be regarded as insignificant. A variation of 15 mm. or more however, might be significant. It was also decided that a single variation could not be regarded as significant, but that 2 or more variations occurring in the same patient could be regarded as being of possible significance.

The records of 83 patients receiving pitressin were scrutinized. Nine were found to be incomplete, leaving 74 complete records. Blood pressure readings were recorded as minimum and maximum systolic, and minimum and maximum diastolic pressure before commencing pitressin, and the same readings after commencing pitressin, i.e. pre- and post- pitressin readings. Of these, it was found that 40 or 54 per cent showed variations in blood pressure after the commencement of pitressin injections. Of these 40 however, only 8 or 10.8 per cent fulfilled both of the criteria mentioned above. Further analysis of these 8 records showed that the blood pressure may vary in any of five different ways. For example:

(a) 2 or 2.7 per cent showed both systolic maximum pressures and diastolic maximum pressures increased after pitressin.

(b) 2, or 2.7 per cent showed both systolic maximum and diastolic maximum pressures decreased after pitressin.

(c) 2, or 2.7 per cent showed systolic maximum pressure increased and diastolic minimum pressure decreased.

(d) 1, or 1.4 per cent showed systolic maximum pressure decreased, diastolic minimum pressure increased.

(e) 1, or 1.4 per cent showed both systolic minimum and maximum pressures increased after pitressin.

Discussion: The 8 patients who showed possibly significant variations in blood pressure after commencing pitressin were respectively:

In group (a), Woman aged 54 years whose pre-pitressin readings were within normal limits, and a woman aged 53 years whose pre-pitressin readings were well above the average for her age group.

In group (b), A woman aged 64 years and a woman aged 54 years both of whose pre-pitressin readings were well above the average for their ages.

In group (c), A 63 year old woman whose pre-pitressin readings fell within the normal range, and a 58 year old woman whose readings were slightly above average before commencing pitressin.

In group (d), A 56 year old woman whose pre-pitressin readings were markedly above average.

In group (e), A 55 year old woman, whose pre-pitressin readings were also elevated.

Out of those 8 patients, therefore, only two can be regarded as showing no evidence of pre-existing hypertension prior to the administration of pitressin. One of those patients is a schizophrenic, hebephrenic type. The other suffers from manic depressive psychosis. Neither has shown any clinical improvement on pitressin alone, although both

From North Carolina State Hospital, Butner, N.C.

have shown slight, though in one case only temporary, improvement on pitressin associated with ECT. Of the other 6 patients, 3 were diagnosed as manic depressive psychosis, and one showed improvement clinically on pitressin. Three were diagnosed as schizophrenic, and no improvement was noted in any of these cases with pitressin.

Conclusion: The pre- and post-pitressin blood pressure readings of 74 patients were studied. Eight patients were found to show variations in blood pressure readings following commencement of pitressin injections, but of these 8, 6 were previously hypertensive, and the 2 remaining patients showed different types of variation in blood pressure following pitressin. There appeared to be no significant correlation between the variations in blood pressure and the clinical course of any of the eight patients.

Author's Note: The foregoing study is published with the permission of Dr. David A. Young, General Superintendent, North Carolina Hospitals Board of Control. Neither Dr. Young nor the Board of Control has any responsibility for any fact or opinion expressed herein.

TABLE I

Pre-pitressin	(a)	(b)	(c)	(d)	(e)
Sys. Max	135	150	140	185	170
Sys. Min	—	—	—	—	105
Dias. Max	80	100	—	—	—
Dias. Min	—	—	60	50	—
Post-pitressin	(a)	(b)	(c)	(d)	(e)
Sys. Max	160	130	180	165	210
Sys. Min	—	—	—	—	120
Dias. Max	95	80	—	—	—
Dias. Min	—	—	45	70	—

Book Review

THE SENSATIONS, THEIR FUNCTIONS, PROCESSES AND MECHANISMS by Henri Pieron (translated by M. H. Pirenne and B. C. Abbott), Yale University Press, New Haven, 1952. 469 pages, $6.00.

Henri Piéron, the author of this scholarly treatise in sensory physiology, is director of the Laboratories of Physiological Psychology at the Sorbonne and editor, since 1912, of L'Année Psychologique. The text itself is, according to the author, an expanded outgrowth of his regular courses of lectures delivered at the College de France since 1923 on the physiology of sensations. Professor Piéron's long experience as a reviewer of scientific papers for L'Année Psychologique and his resultant intimate familiarity with all aspects of this field have immensely enriched the present volume and make it an invaluable and exhaustive reference for workers in sensory physiology. As a research worker of sustained productivity and resourceful originality in sensory spheres he is admirably equipped to evaluate the investigative work of others and to fit their work as well as his own into a broad framework which will most certainly serve as a mature foundation and stimulus for future investigative work particularly in the difficult field of qualitative discriminations.

The text is broadly divided into four parts. Part One is concerned with the nature and meaning of regulation or modulation and, more specifically, with the role of regulatory mechanisms in vital actions. The evolutionary development of sensory systems, factors influencing or imposing specificity in both the stimulus and in the organism's reactions to stimuli, and the general nature of the excitation process are discussed in classical terms with a wealth of fresh documentary detail. Part Two deals methodically and factually with excitatory mechanisms encompassing all the customary modalities. The reader will find especially rewarding the author's excellent discussion of luminous excitation. Part Three introduces more difficult and provocative problems not adequately resolved in this or any other published treatise, namely those concerned with the qualitative aspects of sensory discrimination. Professor Piéron wisely restricts his treatment to the qualitative aspects of visual and auditory sensory experience with only a few brief remarks on odours and tastes. The final section of this book, Part Four, treats of quantitative phenomena, that is with space-time-intensity aspects of sensation. This section is, understandably most detailed since Professor Piéron, in his own investigative work, has himself been occupied with these aspects of the sensory experience.

This work has passages which defy disentanglement as, for example, the following on page 294: "Nevertheless, the use of common objective reference marks, borrowed from stable physical periodicities, is particularly necessary because of the plurality and variability, inter-individual as well as intra-individual, of the subjective times conditioned by multiple and variable biological processes on which depends effectively the current of consciousness, which Bergson believed to be floating freely above the organism." This reviewer has read this particular passage several times because it seemed to pose a genuine challenge, but in spite of the challenge he was ultimately forced to leave the field decisively defeated. Fortunately such passages are few and far between. In general the writing is well turned, the meanings clear. The translators have performed a genuine service in making this material readily available to scientists and research investigators in English speaking countries.

The Sensations will find its greatest usefulness as a source book and ready reference for physiologists and psychologists. For the clinician in Neurology or Psychiatry it makes difficult and technical reading and will probably reach very few. For those, however, who contemplate clinical research studies in the general field of sensory experience it should be consulted particularly since the review of the German and French scientific literature on sensations is admirably comprehensive.

Francis J. Braceland.

Neurological Clinical Pathological Conference

of the
Cincinnati General Hospital
CHARLES D. ARING, M.D., *Editor*
CASE NO. 249534

Presentation

E.H., a Negro girl, was first seen at the age of 5½ years in the Pediatric and Cardiac Clinics in April 1949, where the following history was elicited. In January 1948, the patient had an unusually severe cold which hung on for several weeks. During this period she had had a bout of anorexia, abdominal pain and vomiting; for two or three days one of her knees was red, hot, painful and swollen, but this cleared without residue. A physician had administered penicillin and "some pills" during the acute phase of this illness. The family history was significant in that the patient's mother had been treated for "dermatitis and ulcers of the eyes" in 1943 one sibling had "rheumatic fever," another "a round back and an inferiority complex." The economic status of the family was low.

Examination in April 1949, revealed evidence of mild cardiac enlargement downward and to the left, a systolic thrill over the apex, a blowing grade III systolic and a grade I diastolic murmur, both heard best over the apical region. EKG: auricular damage and primary A-V block. Corrected sedimentation rate (CSR): 9.5. Hemoglobin: 13.2 Gm. WBC: 9950 with 64 per cent lymphocytes and 36 per cent polymorphonuclears. The patient was put on 0.5 Gm. sulfadiazine daily, but it is doubted that she took this regularly since she was brought into clinic only infrequently. She suffered from repeated colds and her temperature was often slightly elevated (99.2 to 100°).

She was next seen in October 1950. Her mother reported that she had had a bad attack of "the flu" during the preceding summer with fever, generalized aches and pains, cough and weight loss. She had not started school in the autumn because of easy fatiguability. Physical examination at this time revealed a blood pressure of 95/60, dental caries, a liver which was one finger-breath and a spleen which was two finger-breadths below the costal margins. Fluoroscopy: widened ventricular diameter with an enlarged pulmonary artery and left auricle. EKG: right ventricular hypertrophy. Sulfadiazine and an iron tonic were prescribed. She was placed on bed rest for a week in December 1950, improving markedly, but then had two grand mal seizures which were described as being mostly on the left side. There was no family history of epilepsy.

In January 1951, the patient was admitted to the hospital for observation. Her heart was as described previously except that now there was no diastolic component to the apical murmur. There were bilateral nasal polyps, enlarged anterior cervical nodes, the liver was still palpable but the spleen had receded. The CSR was 36 mm. per hour, total protein: 9.60 Gm. with 5.10 Gm. of globulin and 4.5 Gm. of albumin, a thermostable anti-Group A Strep hyaluronidase was present, the titer being 417. A neurologic consultant found nothing of significance and recommended that an EEG be done. However, before this could be accomplished, the patient's mother signed her out of the hospital.

The patient was readmitted on March 7, 1951, at the age of 7½ with the complaint of headache and paralyzed left extremities. In the interval between the two admissions there had been frequent nosebleeds, dyspnea on exertion, and some difficulty in controlling the movement of the tongue. Three weeks prior to admission she had stepped on a thumb-tack which penetrated the sole of the left foot but apparently caused no infection. On March 4 a single dose (unknown amount) of gentian violet was given to the patient by her mother as a vermifuge for pinworms. Very soon after she complained of severe generalized headache, was unable to move her left arm and leg, and the right side of her face was "twisted up." She was very drowsy, did not talk, and vomited frequently. On March 6 a physician made a diagnosis of a stroke and recommended hospital care but the mother did not bring her until the following day.

When first seen on March 7, the patient's blood pressure was 104/60, temperature 101°, pulse 96, respirations 32. She was lethargic, lay flat in bed, resisted movement of any part and appeared to be protecting the right side of her face and head. She did not speak except to answer "yes" or "no." There was pallor of all the mucous membranes. Nuchal rigidity was noted. The heart was as described previously but with a third sound in mid-diastole, at times having the quality of a murmur but more often sounding like a third heart tone. P_2 was greater than A_2. There was no pulse deficit but the radial pulses were irregular in intensity. Neurological examination demonstrated a right external rectus palsy, a left supranuclear type of facial paralysis, questionable deviation of the tongue to the left, and a flaccid hemiplegia involving both the left extremities. Deep and superficial reflexes were hypoactive on the left side but no pathological signs were elicited. Lumbar puncture; initial pressure 160 mm; final pressure 80 mm; grossly bloody fluid with 16,750 RBC and 363 WBC per cmm., 95 per cent polymorphonuclears, 5 per cent lymphocytes; 1+ Pandy; 58 mg. per cent sugar. There were 21,000 WBC in the peripheral blood, 98 per cent

polymorphonuclears, 2 per cent lymphocytes. Hemoglobin: 12.0 Gm. BUN: 15 mg. per cent. Blood and spinal fluid cultures were negative, blood Kahn was negative. 100,000 units of penicillin were administered every three hours.

At 3 P.M. on March 8 a focal seizure with involvement of the left side of the face and left upper and lower extremities occurred, following which the patient became comatose. She was somewhat more responsive in the early evening but became apneic at 10 P.M. failing to respond to artificial respiration, caffeine and intracardiac coramine. Death occurred some 36 hours after entry to the hospital.

Differential Diagnosis

*Dr. Samuel Kaplan**: The patient that we are discussing is a negro child first seen at the hospital at the age of 5½ years who died two years later. The history obtained when she was first seen in April 1949 was compatible with acute rheumatic fever during the period of January 1948. We have a history of an upper respiratory infection associated with anorexia, abdominal pain and vomiting.

I should like to make the point that abdominal symptoms, during the course of acute rheumatic fever, are very common. Patients with these complaints may be admitted to surgical wards and be subjected to laparotomy, the diagnosis only becoming evident during the post-operative period. We also have a finding in this patient, that one of her knees was red and hot which, of course, is compatible with acute rheumatic fever. The family background is worth noting because of the high incidence of rheumatic fever in the income group from which this patient apparently came. I want to mention the history of dermatitis and ulcers of the eyes in the patient's mother. I tried to figure out whether this was present during pregnancy and could have affected the developing cardio-vascular system of the patient, but was unable to come to any conclusion because a possible error in calculation of the order of one or two months is of great importance.

Physical examination at the time of the first out-patient admission to this hospital, revealed cardiac signs which were compatible with the diagnosis of acute rheumatic fever. The cardiac enlargement and apical systolic and diastolic murmurs are certainly typical of acute rheumatic fever. An electrocardiogram showed evidence of auricular damage and a primary auriculo-ventricular block. It is somewhat unusual for these signs to persist for such a long time after the initial attack of acute rheumatic fever. The initial attack was in January 1948 and in April 1949 the P-R interval was still prolonged in the EKG. This, of course, does not exclude the diagnosis of rheumatic fever at that time. The normal erythrocyte sedimentation rate and the blood count are compatible with the suspected diagnosis of acute rheumatic fever in January 1948. It is therefore reasonable to assume that the patient did have rheumatic fever which was in a subacute state when she was first seen.

The history obtained during the next admission to the out-patient department was that of a prolonged upper respiratory infection. It is conceivable that the second attack was associated with a subacute form of rheumatic fever which was severe enough to keep the child out of school for a short period. At this time we have the first mention of the patient's blood pressure which was 95/60. I would like to ask whether the record states on which arm this blood pressure was taken and if the femoral artery pulsations were palpable.

Dr. Charles D. Aring: She was seen by Dr. Robert Lyon on October 28, 1950. His note does not mention the femoral vessels, neither is it known whether the right or left arm was used to determine the blood pressure.

Dr. Kaplan: It is known that coarctation of the aorta is not uncommonly associated with congenital aneurysms of the arteries of the brain and autopsy studies have shown that their incidence is about eight per cent in these cases. If this patient's blood pressure was taken in the left arm and if the constriction in the aorta was above the origin of the left subclavin artery, we could still assume that coarctation of the aorta might be present.

Continuing with the signs found on the second out-patient visit we find that hepato- and splenomegaly had developed and that the electrocardiogram was read as showing evidence of right ventricular hypertrophy. Normally in a child the electrocardiogram

*Assistant Clinical Professor of Medicine.

shows a pattern in VI which might be interpreted as right ventricular hypertrophy. Perhaps we could look at the electrocardiogram later. Approximately twenty months after the child was first seen she had two seizures which were described as occurring mainly on the left side. The occurrence of localized seizures in uncomplicated acute rheumatic fever is uncommon.

A few months later the patient was admitted to the hospital for observation. The cardiovascular signs were unchanged, the liver was still palpable, the spleen had receded and the sedimentation rate was elevated. The peculiar elevation of the blood protein was noted on this admission. A change in the blood protein in acute and subacute rheumatic fever may occur, but usually it is a fall in the total level. The albumin-globulin ratio may be affected because of a fall of the albumin fraction. There are many bizarre causes of a high serum globulin, many of which can be automatically excluded in the diagnosis in this patient. Elevation of the serum globulin is seen in liver disease, especially in kala-azar, which I understand does not occur in Cincinnati. Multiple myelomatosis is classically associated with an elevated serum globulin, but this disease usually affects middle aged patients and is unknown in childhood. Nephrosis and lymphogranuloma may give rise to a high globulin but the general picture of this patient does not fit such diagnoses. The final cause of high blood protein which I would like to mention is that of sarcoidosis. Myocardial sarcoid is not as rare a lesion as we sometimes believe. It is of interest that this lesion commonly affects negroes in the second or third decade. I do not want to belabor the diagnosis of sarcoidosis because if one stresses a single point in a clinical pathological conference, he usually meets his Waterloo. I found the blood protein difficult to explain. I believe that the high anti-hyaluronidase titer indicates a recent streptococcal infection and by no means proves the presence of acute rheumatic fever.

We now come to the last admission which was two years after the original outpatient visit. The interim history was associated with recurrent spontaneous epistaxes which frequently occur during the subacute or latent phase of rheumatic fever. Although this symptom may be important, the fact that nasal polypi were found detracts some of its significance because these lesions may have been the source of hemorrhage.

I believe that the history of the thumbtack penetrating the sole of the foot is a red herring and I should be very surprised if tetanus was present in this patient. I have also looked up the question of gentian violet toxicity and I do not think that should be taken seriously even though the patient was given gentian violet for pinworms just prior to the final episode.

During the last admission the cardiac status was unchanged, but the signs in the central nervous system strongly suggest the presence of hemorrhage in the subarachnoid space or rupture of a hemorrhage into one of the ventricles. The presence of the nuchal rigidity and a grossly bloody cerebrospinal fluid tends to confirm this suspicion. To fit the etiology of this cerebral hemorrhage into the preceding history was most difficult. I believe that this complication is not associated with acute rheumatic fever. The question then arises as to whether this patient had subacute bacterial endocarditis with a cerebral embolus which may have been further complicated by the development of a mycotic aneurysm with rupture. Although subacute bacterial endocarditis may masquerade as many different clinical pictures, the history and course of this patient's illness was not that typically associated with a subacute infective process. In particular there was no evidence of continuing pyrexia, anemia, petechial hemorrhages, Osler's nodes, clubbing of the fingers or hematuria. However, a transient splenomegaly was recorded and the final episode could have been due to a cerebral embolus arising from vegetations on the mitral valve.

The next group of conditions to be considered are congenital heart diseases with associated cerebrovascular lesions. Earlier it was mentioned that the commonest congenital heart disease with associated vascular lesions in the brain is coarctation of the aorta. We do not have definite evidence of this anomaly and I believe that the characteristic signs would have been found had they been present.

Another lesion which could have produced this picture is ventricular septal defect with superimposed subacute bacterial endocarditis and embolism to the brain. The statements made previously about subacute bacterial endocarditis would again apply here. The question of congenital heart disease with paradoxial embolization to the brain may arise but there was no evidence of a right to left shunt or peripheral thrombosis from which the embolus might have arisen.

Because of the high blood protein, sarcoidosis is mentioned in the differential diagnosis. Earlier it was stated that sarcoidosis of the heart has been described but the cerebral lesion is usually space-occupying. However, a hemorrhage into a sarcoid tumor may have produced the final episode.

Of the possible diagnoses given I prefer the diagnosis of subacute rheumatic fever with subacute bacterial endocarditis and embolism to the brain with a mycotic aneurysm and cerebral hemorrhage.

My second diagnosis would be congenital heart disease, probably a ventricular septal defect with subacute bacterial endocarditis and embolization to the brain.

Dr. Aring: In the students' discussions they considered acute and subacute rheumatic fever with subacute bacterial endocarditis and congenital heart lesions and sickle cell anemia. I do not recall mention of sarcoidosis. Nineteen students thought that the neurological picture was produced by a mycotic aneurysm. This they localized on the right side of the circle of Willis, but most were not able or did not want to go any further. One mentioned the right middle cerebral artery as a possibility, one the basilar artery. Four students felt that the picture was that of an ordinary cerebral embolism due to subacute bacterial endocarditis, one that it was due to a congenital aneurysm. Two students felt that acute rheumatic fever with cerebral arteritis was operating, so-called rheumatic endarteritis which has been described of late, especially by Bruetsch,[2] one student made a diagnosis of right cavernous sinus thrombosis which was aseptic, and one student, tumor. We could discern no firm opinion in the discussions of three of the students; they listed everything and I suppose we are to take our choice.

The only serious confusion that seemed to prevail among some of the students was about the sixth nerve palsy. This sign they strove valiantly to use in localization, since it was on the right and the hemiplegia was on the left, and the facial weakness which was evidently central in type was also on the left. As Dr. Kaplan said, if a single finding be stressed too much, Waterloo may result. Obviously we haven't told the students convincingly enough that the sixth is the longest cranial nerve, and that frequently it is involved in a secondary fashion. It's involvement need not localize, and if it doesn't fit into your rather exquisite localization you may have to blame sixth nerve palsy on its length, and therefore its exposure to all sorts of stresses and strains along its course from pons to muscle.

Dr. Emanuel Levin: X-rays of the skull were entirely within normal limits, they show no areas of destruction or bone abnormality. The chest is of interest. The initial film showed clear lung fields. There are no abnormalities of the vascular supply and the hilar regions are within normal limits, but there is a definite increase in the transverse diameter of the heart associated with the suggestion of an enlargement of the left auricle as visualized through the silhouette of the heart. The knob is comparatively small in size, but those up close can see that the aorta takes off from the knob without interruption, without any noticeable change in size. Subsequently films show a heart which has changed very little in size except for the last film taken just before death where there may be a slight increase in the size of the heart. In one of these, which fortunately was slightly oblique, we see a left heart border with four curves, an aortic, a pulmonic, and a left auricular curve, and then the large left ventricular curve, which, I believe in this case, is pathognomonic of mitral heart disease.

Discussion of Pathology

Dr. Paul Wozencraft:* The findings of greatest interest in this case, as one might expect, are in the heart and in the brain. This patient's heart weighed 180 grams; the normal heart weight for a child this size and

*Associate Professor of Pathology.

age is somewhere between 100 and 110 grams. So there was considerable hypertrophy. There was rather severe scarring of the mitral valve with shortened chorda tendinea, which probably resulted in more insufficiency than stenosis in this instance.

In the kidneys there were scarred infarcts, so there is evidence that some sort of embolization has been going on, for how long cannot precisely be said, but at least for weeks and possibly months.

In a colored photograph of the heart, great thickening of the mitral valve and also the thickening and shortening of the chorda tendinea may be observed. This represents the classical rheumatic scarring of the mitral valve. An unusual and interesting thing in this instance is the absence of ulceration on the mitral valve, but in the area of McCallum's patch there is a widespread area of roughening and thickening; in the fresh, the prosecutor described this as a very bright red area. Other views of the area showed the roughening and deposits of fibrin some of which appear to be coming off. Again, one sees no ulceration on the valve; the mitral valve is densely scarred but not ulcerated. So an unusual feature of this case is the localization of the endocarditis.

A microphotograph taken through the area of McCallum's patch, showed bacterial endocarditis of the left atrial wall in the area of McCallum's patch. There is fibrin deposit and leucocytes. The blood culture during life was sterile; the post-mortem blood culture was not handled properly and is not worth mention. A gram stain microphotograph of the same area revealed dark staining clumps of organisms, gram positive, short-chain cocci of some sort that we can't identify further by this method.

In the myocardium we find many very active Aschoff bodies. In other sections we see somewhat later stages of the healing Aschoff body. Fibrosis has occurred but there are still scattered lymphocytes in the section; this late lesion was more common than the acute lesions. In photographs of the end state there is still a little activity in this scarring but this very dense onion-peel, perivascular scar is the final stage in healed rheumatic fever.

The brain weighed 1300 grams when it was removed 3 hours after death. There was a thin film of blood over the convolutions of the right cerebral hemisphere, and in the left Sylvian fissure. This blood stain was heaviest about the right internal carotid and middle cerebral arteries whence it extended posteriorly to cover the inferior surfaces of the pons and medulla, and the cerebellar hemispheres.

Careful dissection into the substance of the blood clot revealed a dilatation on the right middle cerebral artery, 1 cm. distal from its origin from the internal carotid artery. A point of rupture measured 3 mm. in diameter. Distal to the aneurysm the right middle cerebral artery was dilated to about twice its calibre and here the lumen of this vessel was filled with fresh thrombus. In the mesial portion of the right temporal lobe, immediately adjacent to the ruptured aneurysm, was a laceration which extended deeply into the tip of the temporal horn of the right lateral ventricle. The tissue adjacent to the laceration in the temporal pole and posterior-lateral aspect of the right frontal lobe, was softened and purplish in color. There were punctate hemorrhages and congestion of vessels in the right lenticular nucleus and the external capsule.

In microscopic examination the right middle cerebral artery was entirely occluded by a thrombus in the stage of early organization; it as well as all layers of the vessel wall was infiltrated with polymorphonuclear leukocytes. The cellular reaction was also predominately acute in the adjacent parenchyma, the cortex containing many polymorphonuclear leukocytes, most of them perivascular in location. Microscopic sections which had been taken from various areas of the brain away from the aneurysmal area revealed leptomeninges distended with red blood cells and polymorphonuclear leukocytes and endothelial cells.

Clinical Diagnosis:

Rheumatic heart disease with subarachnoid hemorrhage secondary to cerebral embolism, right tempero-frontal area.

Doctor Kaplan's Diagnosis:

Subacute rheumatic fever with subacute bacterial endocarditis and embolism to the brain. Mycotic aneurysm and intracerebral hemorrhage.

Anatomical Diagnosis:

Mycotic aneurysm, ruptured, right middle cerebral artery with subarachnoid and intracerebral extension of hemorrhage, right tempero-frontal.

Thrombosis of right middle cerebral artery.

Acute bacterial endocarditis.

Healed rheumatic myocarditis.

Healed infarcts of kidney.

Acute splenitis.

Student: Dr. Kaplan, I wonder if you would comment on the diagnosis of flu during the summertime. The patient had carious teeth and it was known that she had a rheumatic heart. What of the possibility of bacterial endocarditis at that time?

Dr. Kaplan: Certainly it is known that carious teeth can be the source of a bacteremia. It has been shown that if normal persons chew on something hard, for example a rubber stopper, that blood cultures are commonly positive. The organism usually grown is the streptococcus viridans. Therefore it is possible to assume that the portal of entry of the organism in this patient was from the infected teeth.

I think it is of interest that the localization of endocarditis was in McCallum's patch, which was thrombosed, and infected as such an early age, which is not common nor do we find such an intense scarring of the mitral valve at this age. My impression was that usually this severe degree of rheumatic infection was found more frequently after the second decade. A review of the autopsies at the Children's Hospital showed one similar case but without superimposed subacute bacterial endocarditis.

Student: I wonder if the fatigue, fever, etc. might have been compatible with the diagnosis of myocarditis?

Dr. Kaplan: The symptoms produced by acute rheumatic myocarditis are not specific. They are vague and are those that may be associated with many other conditions. I believe that myocarditis can only be diagnosed on physical examination with electrocardiographic and roentgenographic help.

Student: Do you find cerebral embolism more commonly on the left side of the brain than on the right?

Dr. Aring: This was a claim of many years ago; it has long since been disproven by the study of cases coming to autopsy where the distribution is about even as between right and left. Embolism occurs most frequently in the middle cerebral artery or one of its vessels.

Student: Have localizing signs been reported in rheumatic endarteritis in the brain?

Dr. Aring: Yes, they have been written about lately particularly by Bruetsch of Indianapolis. According to Bruetsch, rheumatic endarteritis has a predilection for small meningeal and cortical vessels, the changes resembling those of syphilitic endarteritis. He has described mental charges or convulsions associated with rheumatic endarteritis of the cerebrum.

Dr. Kaplan: I realize that the incidence of death in patients with chorea of rheumatic origin is low. Are there any studies available as to what the pathology of the brain is like in chorea?

Dr. Aring: Such as there are indicate diversity of involvement from case to case, particularly diffuse involvement of gray matter. They have been characterized as toxic changes; endarteritis of smaller vessels with perivascular necrosis has been described. We have come to think, largely by inference I believe, that the predominant neurological signs arise because of involvement of the lower basal ganglia (Luys body).

Student: I would like to ask Dr. Wozencraft what was found in the spleen?

Dr. Wozencraft: Splenitis such as one sees in septic processes.

Student: Was anything found in the liver?

Dr. Wozencraft: The liver was congested.

Student: Does the damage in the liver explain the elevated globulin that was found in this patient?

Dr. Wozencraft: I suppose it could although passive congestion of the liver occurs frequently without elevated globulin. I don't think we have an explanation for the elevated globulin.

Student: Did you find any areas in the brain suggestive of smaller infarcts to explain the convulsive episodes that had occurred months before death?

Dr. Wozencraft: None were found but the fairly old infarcts in the kidney are evidence that there had been embolization going on.

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